CDC
CENTERS FOR DISEASE CONTROL AND PREVENTION

# TUBERCULOSIS INFORMATION

**- Treatment of Tuberculosis Disease**

In most geographical areas, the initial regimen for treating tuberculosis (TB) disease should include four drugs: isoniazid, rifampin, pyrazinamide, and either ethambutol or streptomycin. The regimen can be adjusted when drug susceptibility results become available. In areas where the rate of drug resistance is documented to be less than 4%, three drugs (isoniazid, rifampin, and pyrazinamide) may be adequate for the initial regimen.

The rationale for using four drugs at the beginning of therapy is based on the principle that TB must be treated with multiple drugs to which the infecting organisms are susceptible. This helps prevent the development of drug resistance. However, it can be difficult to select at least two drugs to which the organisms are susceptible when the drug susceptibility results are not known. This is almost always the case at the beginning of therapy. Therefore, CDC recommends that patients be treated initially with a four-drug regimen. Four-drug regimens have been shown to be highly effective, even for isoniazid-resistant organisms.

There are several options for daily and intermittent therapy (Table 1). Dosage recommendations are listed in Table 2.

Table 1
**Regimen Options for the Treatment of TB in Children and Adults**

| Option 1 | Option 2 | Option 3 |
|---|---|---|
| Initial Phase Daily isoniazid, rifampin, pyrazinamide, and either ethambutol or streptomycin for 8 weeks. Ethambutol or streptomycin may be discontinued if TB is susceptible to isoniazid and rifampin. Ethambutol or streptomycin may not be necessary for patients in areas where isoniazid resistance is very low (<4%).<br><br>Continuation Phase If TB is susceptible to isoniazid and rifampin, give isoniazid and rifampin for 16 weeks, either daily, two times weekly, or three times weekly.* | Initial Phase Isoniazid, rifampin, pyrazinamide, and either ethambutol or streptomycin daily for 2 weeks, then two times weekly* for 6 weeks.<br><br>Continuation Phase If TB is susceptible to isoniazid and rifampin, give isoniazid and rifampin two times weekly* for 16 weeks. | Isoniazid, rifampin, pyrazinamide, and either ethambutol or streptomycin three times weekly* for 6 months. |
| For all patients, consult a TB medical expert if drug susceptibility results show resistance to any of the first-line drugs or if the patient remains symptomatic or smear or culture positive after 3 months. | | |

* Directly observed therapy must be used with all regimens administered two or three times weekly.

Table 2

**Dosage Recommendations for the Treatment of TB in Children* and Adults**

| Drugs | Dose in mg/kg [Maximum Dose] | | | | | |
|---|---|---|---|---|---|---|
| | Daily | | Twice-Weekly | | Thrice-Weekly | |
| | Children | Adults | Children | Adults | Children | Adults |
| Isoniazid | 10-20 [300 mg] | 5 [300mg] | 20-40 [900 mg] | 15 [900 mg] | 20-40 [900 mg] | 15 [900 mg] |
| Rifampin | 10-20 [600 mg] | 10mg/kg [600 mg] | 10-20 [600 mg] | 10 [600 mg] | 10-20 [600 mg] | 10 [600 mg] |
| Pyrazinamide | 15-30 [2 gm] | 15-30 [2 gm] | 50-70 [4 gm] | 50-70 [4 gm] | 50-70 [3 gm] | 50-70 [3 gm] |
| Ethambutol** | 15-25 | 15-25 | 50 | 50 | 25-30 | 25-30 |
| Streptomycin | 20-40 [1 gm] | 15 [1 gm] | 25-30 [1.5 gm] | 25-30 [1.5 gm] | 25-30 [1.5 gm] | 25-30 [1.5 gm] |

* Children 12 years of age or younger

** Ethambutol is not recommended for children who are too young to be monitored for changes in their vision. However, ethambutol should be considered for all children who have TB that is resistant to other drugs but susceptible to ethambutol.

Special Situations

*Extrapulmonary TB*. In general, regimens that are adequate for treating pulmonary TB are also effective for treating extrapulmonary TB. However, in some instances, such as lymphatic TB or joint and bone TB, longer therapy may be necessary.

*Pregnancy*. Treatment should not be delayed for pregnant women who have TB disease. The preferred initial regimen is isoniazid, rifampin, and ethambutol. In most cases, pyrazinamide should not be used because sufficient data are not available on how this drug affects the fetus. Streptomycin should not be used because it has been shown to have harmful effects on the fetus. Pregnant women who are taking isoniazid should be given pyridoxine, or vitamin $B_6$.

*Children.* The treatment of TB is essentially the same for children and adults. However, ethambutol is not recommended for children who are too young to be monitored for ocular toxicity (children younger than 8 years old). Infants who are suspected of having TB should be treated immediately because in infants the disease is much more likely to disseminate. Twelve months of therapy is recommended for children with miliary disease, bone and joint disease, or meningitis. Children who have tuberculous meningitis should be treated with 2 months of daily isoniazid, rifampin, pyrazinamide, and streptomycin, followed by 10 months of daily or twice-weekly isoniazid and rifampin.

*Isoniazid-Resistant TB.* A 6-month regimen of isoniazid, rifampin, pyrazinamide, and either ethambutol or streptomycin is effective for the treatment of TB resistant only to isoniazid. When isoniazid resistance is documented during the recommended initial four-drug therapy, isoniazid should be discontinued and the other three drugs should be continued for the entire 6 months of therapy. TB resistant only to isoniazid may also be treated with rifampin and ethambutol for 12 months.

*Multidrug-Resistant TB*. It is more difficult to treat TB that is resistant to isoniazid and rifampin than it is to treat drug-susceptible TB. Therapy for TB resistant to isoniazid and rifampin must continue for 18 to 24 months after the culture becomes negative for *Mycobacterium tuberculosis*. Also, the drugs used to treat drug-resistant TB are less effective and more likely to cause adverse reactions. Clinicians who are not experienced in treating drug-resistant TB should seek expert consultation from the state or local health department.

Side Effects

Antituberculosis drugs are associated with a variety of side effects (Table 3). Before starting therapy, adults should have baseline laboratory tests, and adults and children who are taking ethambutol should have a baseline examination of their visual acuity.

During therapy, clinicians should monitor patients for side effects. They should instruct patients to look for the side effects commonly associated with the drugs they are taking. Also, clinicians should see patients at least once a month and ask them whether they are having side effects.

Patients who remain symptomatic or smear or culture positive after 3 months should be carefully reevaluated, and drug susceptibility tests for these patients should be repeated. Clinicians should consult a TB medical expert if the drug susceptibility results show resistance to any of the first-line drugs.

Table 3
**Major Adverse Reactions of Drugs Used to Treat TB**

| Drug | Major Adverse Reactions | Recommended Regular Monitoring |
|---|---|---|
| Isoniazid | Hepatic enzyme elevation; hepatitis; peripheral neuropathy; mild effects on central nervous system; drug interactions | Measurements of hepatic enzymes if baseline results are abnormal or if symptoms of adverse reactions occur |
| Rifampin* | Gastrointestinal upset; skin eruptions; drug interactions; hepatitis; bleeding problems; flu-like symptoms | Measurements of hepatic enzymes if baseline results are abnormal or if symptoms of adverse reactions occur |
| Pyrazinamide | Hepatitis; rash; gastrointestinal upset; joint aches; hyperuricemia or gout | Measurements of hepatic enzymes if baseline results are abnormal or if symptoms of adverse reactions occur |
| Ethambutol | Ocular toxicity (damage to the optic nerve) | Monthly tests of visual acuity and color vision |
| Streptomycin | Ototoxicity (damage to the nerves of the ear); damage to the kidneys | Hearing tests and kidney function tests |

* Rifampin causes orange discoloration of urine, tears, sweat, and other body fluids. Patients should be advised of this discoloration and of the possible permanent discoloration of soft contact lenses.

Directly Observed Therapy

Nonadherence to treatment is a major cause of drug-resistant TB and treatment failure. The best way to ensure adherence to treatment is to use directly observed therapy. Directly observed therapy means that a health care worker or another designated person watches the patient ingest the prescribed antituberculosis drugs. This method should be considered for all patients because of the difficulty in predicting which patients will adhere to a prescribed treatment regimen. The logistics of directly observed therapy should be tailored to the patient's needs. Intermittent, directly observed regimens have been shown to be a cost-effective method of ensuring that patients complete therapy.

Monitoring Adherence

Pill counting and urine tests have been used to assess whether patients are adhering to therapy for TB. However, the only way to ensure that patients take every dose is to use directly observed therapy.

Antituberculosis Drugs Distributed by CDC

Para-aminosalicylic acid, or PAS, is available from the CDC drug service at (404) 639-3670. Streptomycin is available at no cost from the manufacturer, Pfizer Pharmaceutical. To make an initial request for streptomycin or to request a refill, call Pfizer Pharmaceutical at 1-800-254-4445.

For More Information

To order the following document, call (404) 639-1819.

**CDC. Initial therapy for tuberculosis in the era of multidrug resistance. *MMWR*. 1993;42(RR-7).**

Available July 1, 1994:

American Thoracic Society. Treatment of tuberculosis and tuberculosis infection in adults and children. *Am J Respir Crit Care Med.* 1994;149:1359-1374.

For information about implementing CDC guidelines, call your state health department.

# PUBLIC COMMENT - TUBERCULOSIS FAX SYSTEM

CDC
CENTERS FOR DISEASE CONTROL AND PREVENTION

For a limited time CDC is accepting public comment on the information services you used. We are particularly interested in the areas listed below. If you wish to comment, you may:

**FAX this sheet with your comments to: CDC-VIS/FAX (404) 639-1733, or**
Mail to: CDC, IRMO MS C-15, 1600 Clifton Road, N.E., Atlanta, GA 30333

1. You are
   ____ health care professional
   ____ other

2. Fax sheet(s) you received:
   ____ Tuberculosis (TB): General Information
   ____ TB Infection vs. TB Disease
   ____ Diagnosis of TB Infection (Tuberculin Skin Test) and TB Disease
   ____ Treatment of TB Infection (Preventive Therapy)
   ____ Treatment of TB Disease
   ____ Management of Persons Exposed to Multidrug-Resistant TB
   ____ BCG Vaccine
   ____ Infection Control
   ____ Screening for TB
   ____ TB Morbidity in the United States
   ____ Tuberculosis Educational Materials Order Form

3. Reason you requested fax sheet:
   ____ for general information on topic
   ____ to answer specific question

   If you had a specific question, please describe it:

4. The information met your needs.
   ____ yes
   ____ no
   ____ partially

   If you answered no or partially, please describe your unmet needs:

5. Suggestions for additional information sheets or for improving the system: